I. Proposed Core Hypothesis

Exposure to infectious agents during pregnancy and in the perinatal period (less than 1 month of age) is associated with the development of sensorineural hearing loss (SNHL).

The risks of SNHL are modulated by timing of infection and the genetic polymorphisms of the causative microorganism.

The risks of SNHL are influenced by genes that regulate the immune response to infection and by genes that are responsible for the development of the cochlea, cochlear nerve, medical geniculate nucleus, and auditory cortex.

II. Work Groups

Primary Working Group: Infection, Immunity, and Vaccines

Potential Collaborating Work Groups:

Gene-Environment Interaction
Pregnancy and Infant
Repository

III. Contact

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IV. Public Health Significance.

Hearing loss, either genetic or acquired, represents a potential source of long-term educational, social, and economic disability. Without extensive and effective language training, children with impaired hearing experience significant language delays when compared to their peers with normal hearing (1). Approximately 5,000 infants are born annually in the United States with moderate to profound, bilateral permanent hearing loss (2). Numerous additional infants have varying degrees of unilateral loss. Although universal hearing screening of newborns has been implemented, the long-term public health benefits are undetermined (1,2). The American Academy of Pediatrics currently recommends that at least 95% of all infants should receive hospital-based hearing screening.

In Colorado, a newborn screening program identified 291 infants with congenital hearing loss over an eight-year period (3). Eighty-six of these infants were identified in 1999 (when screening became statewide), corresponding to an occurrence rate of approximately 1 affected child per 650 live-born infants. Of these, the majority of the infants had bilateral sensorineural hearing loss (3). In Utah, a similar, statewide program will identify approximately 50 infants with hearing loss among 45,000 live births annually, or 1 in every 900 infants (4). These data indicate that as many as 6,000 infants in the United States are born annually with sensorineural hearing loss identifiable by newborn screening.

At present, it is estimated that non-syndromic, genetic mutations account for 50% or more of cases of congenital hearing loss. Non-syndromic deafness has been linked to more than 70 chromosome loci, and the genes of more than 20 loci have been identified (5). Of these, mutations in the connexin 26 gene are the most common (5,6), accounting for 40% or more of the non-syndromic, genetic hearing loss (5). Of the remaining 50% of children with hearing loss, approximately one-half are likely the result of intrauterine infections.

For more than 60 years SNHL has also been recognized as a potential complication of intrauterine viral infection. In 1941, the Australian ophthalmologist, Gregg, linked cataracts, congenital heart lesions, and sensorineural hearing loss to maternal infection with the rubella virus (German measles) (7). Although the congenital rubella syndrome has disappeared from nations with compulsory immunization programs, SNHL remains a potential complication of maternal infection with other viral pathogens.

Of these, cytomegalovirus, a betaherpesvirus, appears to be the most common viral cause of SNHL in newborn infants (8). In the United States, 0.4% to 2.5% of newborns shed CMV at birth, and most humans become infected with the virus thereafter, usually without recognizable symptoms (8). Infants with intrauterine infections have traditionally been categorized as “symptomatic” or “asymptomatic” based upon their clinical manifestations at birth. Approximately 10% of the infants with intrauterine CMV infections are asymptomatic at birth, and the remainder are asymptomatic (8). Approximately 10% to 15% of the asymptomatic infants experience SNHL. Approximately 50% of these infants will have SNHL detectable by their first birthday, and the remainder will have hearing loss by their fifth birthday. Because intrauterine CMV infection is highly prevalent in the United States, more than 4000 infants are born annually with CMV-induced SNHL (8-10). This means that more than 200,000 children have experienced CMV-induced hearing loss in the United States alone since 1953, the year CMV was first isolated in cell culture.

V. Need for cohort study.

Studies of CMV-induced hearing loss have been conducted principally at two locations in the United States, Birmingham, Alabama and Houston, TX (9,11). It is uncertain if these observations accurately reflect other population centers in the United States, indicating a need for population-based studies in multiple urban, semi-urban, and rural areas of the country. Moreover, sufficient samples from diverse ethnic and racial backgrounds are required to link CMV-related SNHL to genes that may participate in the

immune responses to viral pathogens or to genes controlling the development of the auditory pathway.

Relatively little is known about other viral teratogens that may induce SNHL in young children. No population-based studies have been performed, for example, to determine the contribution of intrauterine infections with uncommon pathogens, such as lymphocytic choriomeningitis virus (LCM virus), to SNHL (12). A prospective, large population-based cohort study is the only practical means to identify the contribution of these uncommon pathogens to SNHL in childhood.

The overall incidence of congenital CMV infection suggests that approximately 1 in every 1,000 infants may be at risk of CMV-related SNHL. This implies that approximately 100 cases of SNHL will be identified in a cohort of 100,000 live births. Many more infants, between 500 and 1000, will shed CMV at birth, indicating that ample numbers of children will be available to assess the contribution of genetic influences on the risk, severity, and progression of CMV-related SNHL. The numbers of infants with SNHL due to other pathogens is unknown.

VI. Scientific Merit.

The natural history of CMV induced SNHL has been studied in some detail (9). The Alabama group has found that children with CMV-induced hearing loss can experience fluctuating or "new-onset" loss during early childhood (9). Despite these studies, the precise pathogenesis of these late hearing complications of CMV is poorly understood. It is likely that host genetic factors participate in the pathogenesis of CMV-related SNHL. Such genetic factors could include genetic polymorphisms in viral receptors, polymorphisms in immune response genes, or polymorphisms in genes important for hearing development, such as connexin 26. Host genetics could explain why some infants experience severe CMV disease, including high rates of SNHL, and other infants escape sequelae. Moreover, a comprehensive, longitudinal population-based study of the non-syndrome genetic causes of SNHL could suggest that CMV may play a smaller role in SNHL than is currently believed. Knowing the precise etiology of hearing loss has predictive value regarding potential therapies, e.g., cochlear implantation, and recurrence risks.

VII. Potential for Innovative Research.

The past 5 years have brought remarkable achievements in the identification of the genes responsible for non-syndromic hearing loss (13). Similar accomplishments have not been seen, however, in the understanding of the host factors that determine responses to viral pathogens. Given the heterogeneity of outcome observed in infants infected in utero with CMV, it is highly probable that variability in host genes accounts for the facts that only 10% of CMV infected infants have severe disease and only 10% of the infants with silent CMV infections have SNHL. No data are currently available to explain these phenomena. Is it possible, for example, that CMV infection down regulates a host gene and protein product that is essential for the development of normal hearing (14)? Is it possible, also, that new onset or progressive hearing loss has been erroneously

attributed to CMV when host genetic mutations in connexin 26, 30 or other genes are the true causes? These novel questions can be answered by a longitudinal study.

VIII. Feasibility.

Given a cohort of 100,000 newborns, between 400 and 2500 infants with intrauterine CMV infection will be identified. Presently, intrauterine infection with CMV is diagnosed by detection of the virus in fresh samples of urine or saliva using the shell vial assay (8). Urine can be collected by extraction from newborn diapers, minimizing the invasiveness to participating infants. It is likely that methods will be available during the course of this study to assay newborn blood spots for CMV, but at present, the sensitivity and positive predictive value of such assays are unknown. Current technology allows detection of CMV DNA in urine samples by using the polymerase chain reaction (PCR), indicating that archived urine or saliva samples can be utilized.

The incidence of other potential pathogens, such as LCMV, is unknown. Currently, the diagnosis of this infection is made by serologic assay of neonatal blood samples, indicating that the newborn blood spot could be used to establish the incidence of intrauterine infection and the association of infection and complications such as SNHL. Thus, the relationship(s) between subsequent events, such as SNHL, could be established reliably for several agents, including LCM virus and CMV by assaying archived samples of neonatal blood, urine, and saliva.

To detect hearing loss reliably, all infants would undergo newborn screening using otoacoustic emissions (OAE). This can be performed without risk to the infant. Infants who fail their first screening examination would be retested within 1 month. Infants who fail the second OAE screen would require brainstem auditory evoked response testing, a procedure that currently requires sedating the infant. Thus, a modest risk is necessary to confirm SNHL. Children who had normal hearing as neonates would require hearing screens annually until at least 8 years of age to detect late onset hearing loss (9)

IX. References.

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